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Risk Factors for Exposure of Glaucoma Drainage Devices

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Risk Factors for Exposure of Glaucoma Drainage Devices

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ABSTRACT

Objectives: The purpose of this study was to identify risk factors for exposure of glaucoma drainage devices (GDD).

Setting: This retrospective, observational study was conducted in the Eye Clinic of an academic medical center.

Participants: Participants included 1073 consecutive adults who underwent GDD surgery between January 1st, 2005 and January 1st, 2011. Participants were included if chart review indicated GDD surgery during the study period and excluded if at least 12 months of clinical follow-up was not available in the medical record.

Primary outcome measure: The primary outcome measure was exposure of the GDD occurring at least one month after implant surgery. The characteristics of subjects who experienced exposure of the implant were compared to the characteristics of subjects who did not experience exposure.

Results: Of the 1073 subjects having undergone GDD surgery, 67 experienced exposure of the device. Neither the type of GDD, type of patch graft (eye bank sclera, Tutoplast® sclera, and Tutoplast® pericardium), surgeon, location of GDD, number of GDD previously implanted into the eye, nor history of diabetes or uveitis were associated with likelihood of exposure. Women were more likely than men to experience exposure of the GDD (OR 2.004 [95% CI1.170-3.431]) in both univariable (p=0.011) and multivariable (p=0.013) analyses. In survival analysis, exposure of the GDD occurred earlier for women than for men (58 months vs 61 months; p=0.024).White race (versus black) was also associated with increased risk of GDD exposure (OR 1.693 [95% CI 1.011-2.833]) in both univariable (p=0.044) and multivariable (p=0.046) analyses.

Conclusions: Women are two times more likely to experience GDD exposure than men, independent of age. White race is also a risk factor for exposure.

ARTICLE SUMMARY

In a review of 1073 consecutive adult subjects having undergone glaucoma drainage device surgery, characteristics of the 67 subjects who experienced erosion of the device were compared to the subjects who did not experience erosion. Analyses were conducted via univariable and multivariable logistic regression, testing for interactions when appropriate, as well as survival analysis.

Key findings:

- The type of glaucoma drainage device, type of patch graft (eye bank sclera, Tutoplast® sclera, and Tutoplast® pericardium), surgeon, location of the glaucoma drainage device, number of glaucoma drainage devices previously implanted into the eye, history of diabetes or uveitis were not associated with likelihood of exposure.
- Women were more likely than men to experience exposure of the glaucoma drainage device than men (OR 2.004 [95% CI1.170-3.431]) in both univariable (p=0.011) and multivariable (p=0.013) analyses. In survival analysis, exposure of the GDD occurred earlier for women than for men (58 months vs 61 months; p=0.024).
- White race (versus black) was also associated with increased risk of glaucoma drainage device exposure (OR 1.693 [95% CI 1.011-2.833]) in both univariable (p=0.044) and multivariable (p=0.046) analyses.

Strengths and limitations:

- As a retrospective study, all potentially contributing factors may not have been available for review.
- The study includes a larger number of glaucoma drainage device surgeries with greater variety of devices and patch graft materials than has been reported previously and identifies a gender difference in likelihood of exposure that is a new finding.

INTRODUCTION

The use of glaucoma drainage devices (GDD) to manage glaucoma has increased dramatically over the past two decades. Review of Medicare claims data indicates that the number of trabeculectomy surgeries declined by >50% while the number of GDD surgeries increased by >150% from 1995 to 2004.[1] The Tube Versus Trabeculectomy Study has provided evidence that GDD surgery can be at least as effective as trabeculectomy at reducing intraocular pressure and the need for further surgery over a five year time frame.[2] Unfortunately, GDD surgery is not without complications, including erosion of the device through the conjunctiva. Reported rates of GDD exposure in adults range from 3-8% over the first 1-5 years following implant surgery.[3-6] Exposure of the GDD puts the patient at risk for potentially devastating infection;[7] as such, exposure of a GDD warrants surgical revision. Revision of the exposed GDD, however, is challenging. In one large series of revision surgeries for GDD exposure, almost half required additional surgeries following the revision and more than 10% eventually required removal of the implant.[8]

Previously reported risk factors for GDD exposure include inferior versus superior location of the implant,[9 10] prior ocular surgery,[6] and use of specific patch graft materials.[11 12] Most studies investigating risk factors for exposure include only one type of implant or a limited number of patch graft materials. Based on clinical experience, we hypothesized that female gender, older age, white race, and total number of GDD in the operative eye may impart an increased risk of GDD exposure. The purpose of this study was to review the longitudinal outcomes of patients having undergone GDD implant surgery including a broad variety GDD implants, patch graft materials, and surgeons, with the goal of identifying risk factors for exposure of the GDD.

METHODS

This study was conducted with approval from the Duke University Institutional Review Board and in compliance with HIPAA regulations; a waiver of informed consent was granted. A retrospective review was conducted of all GDD surgeries performed on patients at least 18 years of age at the Duke Eye Center between January 1st, 2005 and January 1st, 2011. The Duke Data Unified Content Explorer,[13] a guided query tool for the Duke Enterprise data warehouse, was utilized to identify all surgeries billed for CPT code 66180 (aqueous shunt to extraocular reservoir). Acknowledging that multiple episodes of GDD exposure in the same patient are unlikely to represent independent events, the dataset was further limited to include only one eye and one GDD surgery for

each subject. That is to say, the analysis was conducted at the patient level. Likewise, if a patient underwent multiple surgeries within the study period, only the first GDD surgery performed during the study period was included. In order to optimize capture of GDD exposure events, the dataset was limited to subjects with at least 12 months of clinical follow-up. A single chart abstractor (AL) reviewed the medical record for each subject having undergone surgery, noting demographic information such as age, gender, and race; details of the operation including type and location of GDD implanted, type of patch graft used, and surgeon; and ophthalmic history including history of previous surgery. A random sample of 10% of the charts were reviewed by a second chart abstractor (KWM) and no differences were noted.

The primary outcome for this investigation was GDD exposure. Exposure of the GDD was defined as clinical recognition of exposure of any part of the device occurring more than one month following surgery and requiring repair. We focused on exposure events occurring greater than one month after surgery to differentiate exposure from operative wound dehiscence. The number of months between the initial surgery and exposure was noted. Descriptive statistics were derived, including means, medians, and standard deviations. The associations between potential explanatory factors and the outcome of exposure were analyzed with logistic regression, testing for interactions when appropriate. Odds ratios and confidence intervals were calculated. Survival analysis was used to compare the time to exposure for specific explanatory variables. We analyzed the data using SAS/STAT® software (SAS Institute, Inc., Cary, North Carolina). In all cases, a p value of <0.05 was considered statistically significant.

RESULTS

Between January 1st, 2005 and January 1st, 2011, 1738 GDD surgeries were performed on 1411 adults at the Duke Eye Center. Excluding cases with less than 12 months of follow-up resulted in 1073 individual GDD surgeries for review. During the study period, 67 of these 1073 GDD implants were noted to have become exposed. The characteristics of the total sample and the cases of exposure are described in the Table.

Characteristics of subjects and association with glaucoma drainage device exposure by univariable analysis

Subject Characteristics (n=1073)	Total number (%)	Number with exposure (%)	p-Value	Odds ratio [95% Confidence Interval]
Gender				
Male	483 (45)	20 (4)	0.011	2.00 [1.17-3.43]
Female	590 (55)	47 (8)		
Race				
White	550 (51)	43 (8)	0.044[a]	1.69 [1.01-2.83]
Black	503 (47)	24 (5)		
Other	20 (2)	0		
Diabetes				
Present	300 (28)	23 (34)	0.296	0.76 [0.45-1.28]
Not present	711 (66)	42 (63)		
Unknown	62 (6)	2 (3)		
Uveitis				
History of uveitis	209 (20)	8 (12)	0.410	0.78 [0.44-1.40]
No history of uveitis	649 (60)	47 (70)		
Unknown	215 (20)	12 (18)		
Glaucoma drainage device				
Ahmed	598 (56)	43 (7)	0.203[a]	0.67 [0.42-1.16]
Baerveldt	470 (44)	24 (5)		
Molteno	4 (<1)	0		
Shocket	1 (<1)	0		
Patch graft material				
Eye bank sclera	591(55)	43 (7)	0.174[a]	1.50 [0.85-2.65]
Tutoplast® sclera	363 (34)	18 (5)		
Sclera NOS[b]	75 (7)	4 (5)		
Single-layer Tutoplast® pericardium	39 (4)	2 (5)		
Double-layer Tutoplast® pericardium	14 (1)	0		
Unknown	1 (<1)	0		
Location				
Superior	991(92)	62 (6)	0.955	1.03 [0.40-2.63]
Inferior	82 (8)	5 (6)		
Total number of glaucoma drainage devices in eye				
One	817 (76)	49	0.125[c]	0.65 [0.37-1.13]
Two	175 (16)	16		
Three	24 (2)	2		
Four	1 (<1)	0		

	Value		p-Value
Age (years, mean±SD; median)	64±16; 66	65±16; 69	0.335

[a]p-values and odds ratios derived from Fishers Exact test for comparison of exposure for italicized variables (other variables in that category with insufficient data points for analysis) .
[b]NOS = not otherwise specified
[c]p-value for comparison of a single glaucoma drainage device versus multiple glaucoma drainage devices in the same eye.

The duration of follow-up after GDD surgery ranged from 12 to 84 months, mean 41 months, median 37 months. The GDD implantation surgeries were performed by 10 different glaucoma fellowship-trained surgeons and there was not a significant association between individual surgeon and likelihood of GDD exposure (p=0.202). In univariable analyses of potential explanatory variables including type of GDD, type of patch graft, total number of GDD in the eye, and location of GDD, only female gender (p=0.011) and white race (p=0.044) were associated with likelihood of exposure (Table). Women having undergone GDD surgery had twice the odds of experiencing exposure than men who underwent GDD surgery (OR 2.00 [95% CI 1.17-3.43]). We considered that the association between gender and exposure might be related to age, as the women in the sample were, on average, older at the time of surgery than the men (mean age of women 66 years, mean age of men 61 years, p=0.001). The test of interaction between age and gender was significant (p=0.025), implying that age influenced the association between gender and exposure differently for women compared to men. As such, separate analyses were performed for men and women with regards to the association between age and exposure, revealing that increasing age was associated with increased likelihood of GDD exposure for men (p=0.038), but not for women (p=0.394).

Multivariable analysis

The interaction between age and race was not significant (p=0.109); as such, age, race, and gender were considered together as explanatory factors for the outcome of exposure. In this multivariable logistic regression model, age was not associated with exposure (p=0.657); black race (p=0.046) and female gender (p=0.013) remained significantly associated with likelihood of exposure. The odds of a white female experiencing exposure of the GDD were 3.88 times that of a black male experiencing exposure.

Survival analysis

To account for duration of follow-up, the relationship between potential explanatory variables and the outcome of GDD exposure was also queried by survival analysis. The mean time from GDD implant surgery to GDD exposure was 25 ± 19 months. The mean time to exposure for females was 23 ± 18 months and for males was 31 ± 20 months. Survival analysis revealed that females experienced exposure of the GDD earlier in the course of follow-up than men (p=0.024, Figure). White patients experienced exposure earlier than African American patients (0.026). Survival of the GDD without exposure was not associated with location of the GDD, history of multiple GDD, diabetes, uveitis, type of glaucoma, or type of patch graft used (p=0.239-0.669).

DISCUSSION

Glaucoma drainage device surgery is becoming increasingly common,[1] and is a valuable tool in the management of glaucoma. Exposure of the implant, however, is one of the more frequent[3-6] and challenging complications of GDD surgery.[7 8] To better inform both surgeons and patients about the risks and benefits of GDD surgery, we need a clearer understanding of the risk factors associated with exposure of the implant.

Most of the studies which have provided evidence for rates of GDD exposure have included only one type of implant, such as the Baerveldt,[3 5] or Ahmed.[6 10] One study of exposure outcomes included both Baerveldt and Ahmed implants but focused primarily on outcome differences based on patch graft materials.[11] Our study included 598 (56%) Ahmed and 470 (44%) Baerveldt GDD implants. We did not find a difference in exposure outcomes related to type of GDD: 43 (7%) of the subjects with Ahmed implants experienced exposure compared to 24 (5%) of the subjects with Baerveldt implants (p=0.203). Exposure rates for both types of implants fell within the range of exposure rates previously published. [3-6]

Previous studies have compared the exposure-related outcomes for specific patch graft materials and found that single-layer pericardium is associated with greater risk of exposure than double-layer pericardium[11] and pericardial patch grafts in general are associated with greater likelihood of exposure than corneal patch grafts.[12] Some studies, however, have failed to find an association between patch graft material and exposure rates.[4] In our study, a variety of patch graft materials were employed: primarily eye bank sclera (n=591, 55%), Tutoplast® (IOP Ophthalmics, Costa Mesa, California) sclera (n= 363, 34%) and to a lesser extent, single (n=39, 4%) and double-layer (n=14, 1%) Tutoplast® pericardium. The numbers of subjects receiving pericardial patch grafts were too small for adequate analysis, but there were no incidences of exposure in our double layer pericardial patch group as there were none in the 59 cases in Moster's study.[11] We did not find an association between the likelihood of exposure for subjects receiving eye bank sclera (n= 43 exposure, 7%) compared to subjects receiving Tutoplast® sclera (n= 18 exposures, 5%; p=0.174). Although failure to detect

a difference does not mean that a differential likelihood of exposure does not exist, given the similar rates of exposure between subjects with eye bank sclera and subjects with Tutoplast® sclera, a much larger sample would be needed to detect significant difference. For example, based on the rates of exposure in our study , we estimate that 2327 subjects receiving eye bank and 2327 subjects receiving Tutoplast® sclera would be needed to have 90% power to detect a significant difference in likelihood of exposure, with α=0.05.

Reports of GDD exposure related to location of the implant have varied. In a series of Ahmed GDD surgeries, implants placed in the inferior quadrants were more likely to expose than implants located superiorly.[10] Another study of Ahmed implants, however, found higher rates of early wound dehiscence for GDD implants located inferiorly, but no association between location and later GDD exposure.[9] We also did not find a difference in exposure for inferior (n= 5 exposures, 6%) versus superior location of the device (n= 62 exposures, 6%; p=0.955). Furthermore, we did not find a difference in the likelihood of exposure for GDD implants in eyes with a single implant (n= 49 exposures, 6%) compared to eyes with pre-existing GDD prior to the surgery included in the study (n= 18 exposures, 9%; p= 0.125). We purposely, however, only considered the first GDD surgery within the study period for each subject, so it is possible that we underestimated the rates of exposure for subjects with multiple implants by excluding subsequent GDD surgeries and exposure events in the same subject.

We observed that women had twice the odds of experiencing exposure of the GDD compared to men. In attempts to understand this association, we considered that this finding may be confounded by age, as the women in the study population were, on average, older at the time of surgery than the men. Indeed, the test of interaction between age and gender with regards to likelihood of GDD was significant, indicating that age influences the likelihood of exposure differently for men and women. For men, increasing age inferred a greater likelihood of exposure; multivariable analysis revealed that women, however, were more likely to experience exposure of the GDD than men regardless of age. Moreover, in survival analysis, women experienced GDD exposure earlier in the course of follow-up than men. A gender-related difference in GDD exposure is a new finding: in a study of 11 cases of GDD exposure and 44 subjects with GDD and without exposure, age and gender were not related to likelihood of exposure of the device.[6] The number of subjects included in our study is, however, substantially larger, improving our power to detect outcome differences.

We found that white race (compared to black race) was associated with greater likelihood of GDD exposure, although the association was not as strong (OR 1.69 [95% CI 1.01-2.83]). When considered together in a multivariable model, white race (p=0.046) and female gender (p=0.013) remained significantly associated with GDD

exposure.   Although, to our knowledge, no previous studies have found race to be a risk factor for primary exposure of the GDD, interestingly, black race was a risk factor for requiring multiple surgeries following repair of GDD exposure in a series of exposure cases.[8] The same study also found diabetes to be a risk factor for failure of primary revision of an exposed GDD. We did not find an association between diabetes and GDD exposure. Presence or absence of diabetes was determined by review of the problem list in our study, rather than laboratory tests, and some subjects with diabetes may have been classified as nondiabetics. Consistent with our findings, however, investigators in Korea did not find an association between diabetes and GDD exposure.[6]

We considered potential factors that might explain the increased likelihood of GDD exposure in women. Friction of the implant against the ocular tissues may contribute to late exposure of the GDD. In general, the orbital dimensions of women are smaller than men, with lower average height of the orbit and width of the orbital fissure for women compared to men.[14] Rates of GDD exposure are higher in children than in adults, supporting the theory that a "tight" orbit is associated with increased likelihood of exposure.[15] A mechanically tighter orbit may contribute to the racial differences in exposure outcomes noted in our study. On average, the palpebral fissure width is greater for blacks than for whites.[16]

Repetitive microtrauma may compromise conjunctival integrity, increasing the risk for exposure. Ocular dryness may exacerbate friction between the eyelids and ocular surface. The median age at surgery for the subjects in our study was 66 years, suggesting that many women were post-menopausal and may have hormone-related dry eye syndrome. A prospective study quantifying dry eye in patients undergoing GDD surgery may help determine if dry eye influences the association between female gender and GDD exposure.

Our study has several limitations. Some patients may have experienced GDD exposure more than one year after surgery and have been treated elsewhere. Our dataset was limited to the history in the medical record and documentation may not always be complete. For example, we did not find an association between uveitis and exposure. The history of uveitis may not have been recorded for every patient, however. In children, uveitis is a risk factor for GDD exposure.[15] Likewise, we could not examine the contribution of dry eye disease. Similarly, we limited our surgical history to previous glaucoma surgeries; other prior conjunctival surgeries may be associated with GDD exposure, but was not uniformly recorded for each subject.

We purposefully limited our study to cases of exposure occurring more than one month from surgery to exclude operative wound dehiscence; accordingly, the findings should not be extrapolated to include early exposures. Indeed, other studies have found

alternative risk factors for early wound dehiscence.[9] We chose to exclude repeat surgeries in the same patient in order to not over-represent patient-specific characteristics which might predispose an individual to exposure of the GDD. As such, the finding that women are at increased risk for exposure is even more robust.

To our knowledge, this is the largest series of GDD surgeries reported which includes a variety of types of GDD implants and patch graft materials. As GDD surgeries become an increasingly common event in the management of glaucoma, further study is needed to understand why women are at greater risk of GDD exposure and what can be done to mitigate this risk.
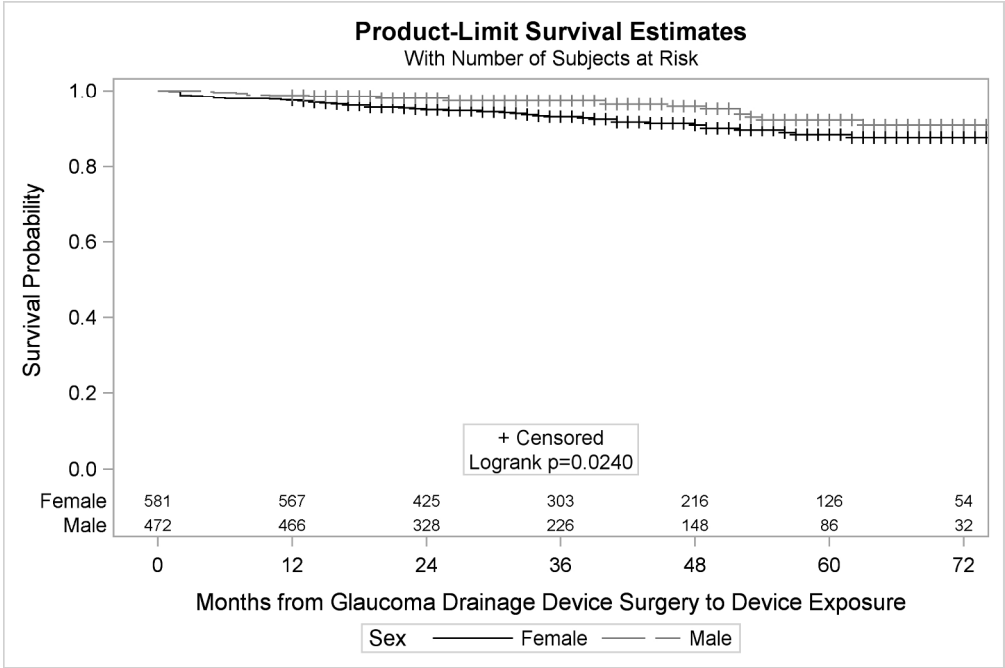
ACKNOWLEDGEMENTS

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Product-Limit Survival Estimates
With Number of Subjects at Risk

	0	12	24	36	48	60	72
Female	581	567	425	303	216	126	54
Male	472	466	328	226	148	86	32

+ Censored
Logrank p=0.0240

Months from Glaucoma Drainage Device Surgery to Device Exposure

Sex ——— Female — — Male

Survival probabilities for tube exposure for females and males

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract ✓	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale ✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives ✓	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design ✓	4	Present key elements of study design early in the paper
Setting ✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants ✓	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables ✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement ✓	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias ✓	9	Describe any efforts to address potential sources of bias
Study size ✓	10	Explain how the study size was arrived at
Quantitative variables ✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods ✓	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
✓		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
✓		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
✓		*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
✓		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
✓		

Discussion

Key results	✓ 18	Summarise key results with reference to study objectives
Limitations	✓ 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓		
Generalisability ✓	21	Discuss the generalisability (external validity) of the study results

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
✓		

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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ABSTRACT

Objectives: The purpose of this study was to identify risk factors for exposure of glaucoma drainage devices (GDD).

Setting: This retrospective, observational study was conducted in the Eye Clinic of an academic medical center.

Participants: Participants included 1073 consecutive adults who underwent GDD surgery between January 1st, 2005 and January 1st, 2011. Participants were included if chart review indicated GDD surgery during the study period and excluded if at least 12 months of clinical follow-up was not available in the medical record.

Primary outcome measure: The primary outcome measure was exposure of the GDD occurring at least one month after implant surgery. The characteristics of subjects who experienced exposure of the implant were compared to the characteristics of subjects who did not experience exposure.

Results: Of the 1073 subjects having undergone GDD surgery, 67 experienced exposure of the device. Neither the type of GDD, type of patch graft (eye bank sclera, Tutoplast® sclera, and Tutoplast® pericardium), surgeon, location of GDD, number of GDD previously implanted into the eye, nor history of diabetes or uveitis were associated with likelihood of exposure. Women were more likely than men to experience exposure of the GDD (OR 2.004 [95% CI1.170-3.431]) in both univariable (p=0.011) and multivariable (p=0.013) analyses. In survival analysis, exposure of the GDD occurred earlier for women than for men (58 months vs 61 months; p=0.024).White race (versus black) was also associated with increased risk of GDD exposure (OR 1.693 [95% CI 1.011-2.833]) in both univariable (p=0.044) and multivariable (p=0.046) analyses.

Conclusions: Women are two times more likely to experience GDD exposure than men, independent of age. White race is also a risk factor for exposure.

ARTICLE SUMMARY

In a review of 1073 consecutive adult subjects having undergone glaucoma drainage device surgery, characteristics of the 67 subjects who experienced erosion of the device were compared to the subjects who did not experience erosion. Analyses were conducted via univariable and multivariable logistic regression, testing for interactions when appropriate, as well as survival analysis.

Key findings:

- The type of glaucoma drainage device, type of patch graft (eye bank sclera, Tutoplast® sclera, and Tutoplast® pericardium), surgeon, location of the glaucoma drainage device, number of glaucoma drainage devices previously implanted into the eye, history of diabetes or uveitis were not associated with likelihood of exposure.
- Women were more likely than men to experience exposure of the glaucoma drainage device than men (OR 2.004 [95% CI1.170-3.431]) in both univariable (p=0.011) and multivariable (p=0.013) analyses. In survival analysis, exposure of the GDD occurred earlier for women than for men (58 months vs 61 months; p=0.024).
- White race (versus black) was also associated with increased risk of glaucoma drainage device exposure (OR 1.693 [95% CI 1.011-2.833]) in both univariable (p=0.044) and multivariable (p=0.046) analyses.

Strengths and limitations:

- As a retrospective study, all potentially contributing factors may not have been available for review.
- The study includes a larger number of glaucoma drainage device surgeries with greater variety of devices and patch graft materials than has been reported previously and identifies a gender difference in likelihood of exposure that is a new finding.

INTRODUCTION

The use of glaucoma drainage devices (GDD) to manage glaucoma has increased dramatically over the past two decades. Review of Medicare claims data indicates that the number of trabeculectomy surgeries declined by >50% while the number of GDD surgeries increased by >150% from 1995 to 2004.[1] The Tube Versus Trabeculectomy Study has provided evidence that GDD surgery can be at least as effective as trabeculectomy at reducing intraocular pressure and the need for further surgery over a five year time frame.[2] Unfortunately, GDD surgery is not without complications, including erosion of the device through the conjunctiva. Reported rates of GDD exposure in adults range from 3-8% over the first 1-5 years following implant surgery.[3-7] Exposure of the GDD puts the patient at risk for potentially devastating infection;[8] as such, exposure of a GDD warrants surgical revision. Revision of the exposed GDD, however, is challenging. In one large series of revision surgeries for GDD exposure, almost half required additional surgeries following the revision and more than 10% eventually required removal of the implant.[9]

Previously reported risk factors for GDD exposure include inferior versus superior location of the implant,[10 11] prior[4] or concurrent[3] ocular surgery, use of specific patch graft materials,[12 13] and Hispanic race.[14] Most studies investigating risk factors for exposure include only one type of implant or a limited number of patch graft materials. Based on clinical experience, we hypothesized that female gender, older age, white race, and total number of GDD in the operative eye may impart an increased risk of GDD exposure. The purpose of this study was to review the longitudinal outcomes of patients having undergone GDD implant surgery including a broad variety GDD implants, patch graft materials, and surgeons, with the goal of identifying risk factors for exposure of the GDD.

METHODS

This study was conducted with approval from the Duke University Institutional Review Board and in compliance with HIPAA regulations; a waiver of informed consent was granted. A retrospective review was conducted of all GDD surgeries performed on patients at least 18 years of age at the Duke Eye Center between January 1st, 2005 and January 1st, 2011. The Duke Data Unified Content Explorer,[15] a guided query tool for the Duke Enterprise data warehouse, was utilized to identify all surgeries billed for CPT code 66180 (aqueous shunt to extraocular reservoir). Acknowledging that multiple episodes of GDD exposure in the same patient are unlikely to represent independent events, the dataset was further limited to include only one eye and one GDD surgery for

each subject. That is to say, the analysis was conducted at the patient level. Likewise, if a patient underwent multiple surgeries within the study period, only the first GDD surgery performed during the study period was included. In order to optimize capture of GDD exposure events, the dataset was limited to subjects with at least 12 months of clinical follow-up. A single chart abstractor (AL) reviewed the medical record for each subject having undergone surgery, noting demographic information such as age, gender, and race; details of the operation including type and location of GDD implanted, type of patch graft used, and surgeon; and ophthalmic history including history of previous surgery. A random sample of 10% of the charts were reviewed by a second chart abstractor (KWM) and no differences were noted.

The primary outcome for this investigation was GDD exposure. Exposure of the GDD was defined as clinical recognition of exposure of any part of the device occurring more than one month following surgery and requiring repair. We focused on exposure events occurring greater than one month after surgery to differentiate exposure from operative wound dehiscence. The number of months between the initial surgery and exposure was noted. Descriptive statistics were derived, including means, medians, and standard deviations. The associations between potential explanatory factors and the outcome of exposure were analyzed with logistic regression, testing for interactions when appropriate. Odds ratios and confidence intervals were calculated. Survival analysis was used to compare the time to exposure for specific explanatory variables. We analyzed the data using SAS/STAT® software (SAS Institute, Inc., Cary, North Carolina). In all cases, a p value of <0.05 was considered statistically significant.

RESULTS

Between January 1st, 2005 and January 1st, 2011, 1738 GDD surgeries were performed on 1411 adults at the Duke Eye Center. Excluding cases with less than 12 months of follow-up resulted in 1073 individual GDD surgeries for review. During the study period, 67 of these 1073 GDD implants were noted to have become exposed. The characteristics of the total sample and the cases of exposure are described in the Table.

Characteristics of subjects and association with glaucoma drainage device exposure by univariable analysis

Subject Characteristics (n=1073)	Total number (%)	Number with exposure (%)	p-Value	Odds ratio [95% Confidence Interval]
Gender				
Male	483 (45)	20 (4)	0.011	2.00 [1.17-3.43]
Female	590 (55)	47 (8)		
Race				
White	550 (51)	43 (8)	0.044[a]	1.69 [1.01-2.83]
Black	503 (47)	24 (5)		
Other	20 (2)	0		
Diabetes				
Present	300 (28)	23 (34)	0.296	0.76 [0.45-1.28]
Not present	711 (66)	42 (63)		
Unknown	62 (6)	2 (3)		
Uveitis				
History of uveitis	209 (20)	8 (12)	0.410	0.78 [0.44-1.40]
No history of uveitis	649 (60)	47 (70)		
Unknown	215 (20)	12 (18)		
Glaucoma drainage device				
Ahmed	598 (56)	43 (7)	0.203[a]	0.67 [0.42-1.16]
Baerveldt	470 (44)	24 (5)		
Molteno	4 (<1)	0		
Shocket	1 (<1)	0		
Patch graft material				
Eye bank sclera	591(55)	43 (7)	0.174[a]	1.50 [0.85-2.65]
Tutoplast® sclera	363 (34)	18 (5)		
Sclera NOS[b]	75 (7)	4 (5)		
Single-layer Tutoplast® pericardium	39 (4)	2 (5)		
Double-layer Tutoplast® pericardium	14 (1)	0		
Unknown	1 (<1)	0		
Location				
Superior	991(92)	62 (6)	0.955	1.03 [0.40-2.63]
Inferior	82 (8)	5 (6)		
Total number of glaucoma drainage devices in eye				
One	817 (76)	49	0.125[c]	0.65 [0.37-1.13]
Two	175 (16)	16		
Three	24 (2)	2		
Four	1 (<1)	0		

	Value		p-Value
Age (years, mean±SD; median)	64±16; 66	65±16; 69	0.335

[a]p-values and odds ratios derived from Fishers Exact test for comparison of exposure for italicized variables (other variables in that category with insufficient data points for analysis) .
[b]NOS = not otherwise specified
[c]p-value for comparison of a single glaucoma drainage device versus multiple glaucoma drainage devices in the same eye.

The duration of follow-up after GDD surgery ranged from 12 to 84 months, mean 41 months, median 37 months. The GDD implantation surgeries were performed by 10 different glaucoma fellowship-trained surgeons and there was not a significant association between individual surgeon and likelihood of GDD exposure (p=0.202). In univariable analyses of potential explanatory variables including type of GDD, type of patch graft, total number of GDD in the eye, and location of GDD, only female gender (p=0.011) and white race (p=0.044) were associated with likelihood of exposure (Table 1). Women having undergone GDD surgery had twice the odds of experiencing exposure than men who underwent GDD surgery (OR 2.00 [95% CI 1.17-3.43]). We considered that the association between gender and exposure might be related to age, as the women in the sample were, on average, older at the time of surgery than the men (mean age of women 66 years, mean age of men 61 years, p=0.001). The test of interaction between age and gender was significant (p=0.025), implying that age influenced the association between gender and exposure differently for women compared to men. As such, separate analyses were performed for men and women with regards to the association between age and exposure, revealing that increasing age was associated with increased likelihood of GDD exposure for men (p=0.038), but not for women (p=0.394).

Multivariable analysis

The interaction between age and race was not significant (p=0.109); as such, age, race, and gender were considered together as explanatory factors for the outcome of exposure. In this multivariable logistic regression model, age was not associated with exposure (p=0.657); white race (p=0.046) and female gender (p=0.013) remained significantly associated with likelihood of exposure. The odds of a white female experiencing exposure of the GDD were 3.88 times that of a black male experiencing exposure.

Survival analysis

To account for duration of follow-up, the relationship between potential explanatory variables and the outcome of GDD exposure was also queried by survival analysis. The mean time from GDD implant surgery to GDD exposure was 25 ± 19 months. The mean time to exposure for females was 23 ± 18 months and for males was 31 ± 20 months. Survival analysis revealed that females experienced exposure of the GDD earlier in the course of follow-up than men (p=0.024, Figure). White patients experienced exposure earlier than African American patients (0.026). Survival of the GDD without exposure was not associated with location of the GDD, history of multiple GDD, diabetes, uveitis, type of glaucoma, or type of patch graft used (p=0.239-0.669).

DISCUSSION

Glaucoma drainage device surgery is becoming increasingly common,[1] and is a valuable tool in the management of glaucoma. Exposure of the implant, however, is one of the more frequent[2-4 6] and challenging complications of GDD surgery.[8 9] To better inform both surgeons and patients about the risks and benefits of GDD surgery, we need a clearer understanding of the risk factors associated with exposure of the implant.

Most of the studies which have provided evidence for rates of GDD exposure have included only one type of implant, such as the Baerveldt,[6 7] or Ahmed.[4 10] One study of exposure outcomes included both Baerveldt and Ahmed implants but focused primarily on outcome differences based on patch graft materials.[11] Another recent study included multiple types of implants and did not find a difference in exposure rates.[3] Our study included 598 (56%) Ahmed and 470 (44%) Baerveldt GDD implants. We did not find a difference in exposure outcomes related to type of GDD: 43 (7%) of the subjects with Ahmed implants experienced exposure compared to 24 (5%) of the subjects with Baerveldt implants (p=0.203). Exposure rates for both types of implants fell within the range of exposure rates previously published.[3-7]

Previous studies have compared the exposure-related outcomes for specific patch graft materials and found that single-layer pericardium is associated with greater risk of exposure than double-layer pericardium[13] and pericardial patch grafts in general are associated with greater likelihood of exposure than corneal patch grafts.[12] Some studies, however, have failed to find an association between patch graft material and exposure rates.[3 4] In our study, a variety of patch graft materials were employed: primarily eye bank sclera (n=591, 55%), Tutoplast® (IOP Ophthalmics, Costa Mesa, California) sclera (n= 363, 34%) and to a lesser extent, single (n=39, 4%) and double-layer (n=14, 1%) Tutoplast® pericardium. The numbers of subjects receiving pericardial patch grafts were too small for adequate analysis, but there were no incidences of exposure in our double layer pericardial patch group as there were none in the 59 cases in Moster's study.[13] We did not find an association between the likelihood of

exposure for subjects receiving eye bank sclera (n= 43 exposure, 7%) compared to subjects receiving Tutoplast® sclera (n= 18 exposures, 5%; p=0.174). Although failure to detect a difference does not mean that a differential likelihood of exposure does not exist, given the similar rates of exposure between subjects with eye bank sclera and subjects with Tutoplast® sclera, a much larger sample would be needed to detect significant difference. For example, based on the rates of exposure in our study , we estimate that 2327 subjects receiving eye bank and 2327 subjects receiving Tutoplast® sclera would be needed to have 90% power to detect a significant difference in likelihood of exposure, with α=0.05.

Reports of GDD exposure related to location of the implant have varied. In a series of Ahmed GDD surgeries, implants placed in the inferior quadrants were more likely to expose than implants located superiorly.[10] Another study of Ahmed implants, however, found higher rates of early wound dehiscence for GDD implants located inferiorly, but no association between location and later GDD exposure.[11] We also did not find a difference in exposure for inferior (n= 5 exposures, 6%) versus superior location of the device (n= 62 exposures, 6%; p=0.955). Furthermore, we did not find a difference in the likelihood of exposure for GDD implants in eyes with a single implant (n= 49 exposures, 6%) compared to eyes with pre-existing GDD prior to the surgery included in the study (n= 18 exposures, 9%; p= 0.125). We purposely, however, only considered the first GDD surgery within the study period for each subject, so it is possible that we underestimated the rates of exposure for subjects with multiple implants by excluding subsequent GDD surgeries and exposure events in the same subject. We did not investigate concurrent ophthalmic surgery as a risk factor for GDD exposure, although this has recently been reported to be a significant factor associated with GDD exposure.[3]

We observed that women had twice the odds of experiencing exposure of the GDD compared to men. In attempts to understand this association, we considered that this finding may be confounded by age, as the women in the study population were, on average, older at the time of surgery than the men. Indeed, the test of interaction between age and gender with regards to likelihood of GDD was significant, indicating that age influences the likelihood of exposure differently for men and women. For men, increasing age inferred a greater likelihood of exposure; multivariable analysis revealed that women, however, were more likely to experience exposure of the GDD than men regardless of age. Moreover, in survival analysis, women experienced GDD exposure earlier in the course of follow-up than men. A gender-related difference in GDD exposure is a new finding: in a study of 11 cases of GDD exposure and 44 subjects with GDD and without exposure, age and gender were not related to likelihood of exposure of the device.[4] Likewise, in a recent study of 339 eyes of 332 subjects with GDD surgery including 28 eyes with GDD exposure, gender was not associated with

likelihood of exposure.[3] Our study, however, defined exposure as occurring at least one month post-operatively, and it is possible that female gender is a more important risk factor for later exposure than in early would dehiscence. The number of subjects included in our study is also larger, improving our power to detect outcome differences.

We found that white race (compared to black race) was associated with greater likelihood of GDD exposure, although the association was not as strong (OR 1.69 [95% CI 1.01-2.83]). When considered together in a multivariable model, white race (p=0.046) and female gender (p=0.013) remained significantly associated with GDD exposure. In a recent case control study of GDD exposures, Koval et al found Hispanic race (versus non Hispanic ethnicity including black and white subjects), to be a risk factor for exposure.[14] Our study population did not include enough persons of Hispanic descent for analysis. Koval and colleagues matched controls to cases based on gender, so the influence of gender on exposure risk as not explored. Although, to our knowledge, no previous studies have found black race to be a risk factor for primary exposure of the GDD, interestingly, black race was a risk factor for requiring multiple surgeries following repair of GDD exposure in a series of exposure cases.[9] The same study also found diabetes to be a risk factor for failure of primary revision of an exposed GDD. We did not find an association between diabetes and GDD exposure. Presence or absence of diabetes was determined by review of the problem list in our study, rather than laboratory tests, and some subjects with diabetes may have been classified as nondiabetics. Consistent with our findings, however, investigators in Korea did not find an association between diabetes and GDD exposure.[4]

We considered potential factors that might explain the increased likelihood of GDD exposure in women. Friction of the implant against the ocular tissues may contribute to late exposure of the GDD. In general, the orbital dimensions of women are smaller than men, with lower average height of the orbit and width of the orbital fissure for women compared to men.[16] Rates of GDD exposure are higher in children than in adults, supporting the theory that a "tight" orbit is associated with increased likelihood of exposure.[17] A mechanically tighter orbit may contribute to the racial differences in exposure outcomes noted in our study. On average, the palpebral fissure width is greater for blacks than for whites.[18]

Repetitive microtrauma may compromise conjunctival integrity, increasing the risk for exposure. Ocular dryness may exacerbate friction between the eyelids and ocular surface. The median age at surgery for the subjects in our study was 66 years, suggesting that many women were post-menopausal and may have hormone-related dry eye syndrome. A prospective study quantifying dry eye in patients undergoing GDD surgery may help determine if dry eye influences the association between female gender and GDD exposure.

Our study has several limitations. Some patients may have experienced GDD exposure more than one year after surgery and have been treated elsewhere. Our dataset was limited to the history in the medical record and documentation may not always be complete. For example, we did not find an association between uveitis and exposure. The history of uveitis may not have been recorded for every patient, however. In children, uveitis is a risk factor for GDD exposure.[17] Likewise, we could not examine the contribution of dry eye disease. Similarly, we limited our surgical history to previous GDD surgery; other prior conjunctival surgeries may be associated with GDD exposure, but was not uniformly recorded for each subject, especially subjects who may have had surgeries prior to treatment at our institution.

We purposefully limited our study to cases of exposure occurring more than one month from surgery to exclude operative wound dehiscence; accordingly, the findings should not be extrapolated to include early exposures. Indeed, other studies have found alternative risk factors for early wound dehiscence.[11] We chose to exclude repeat surgeries in the same patient in order to not over-represent patient-specific characteristics which might predispose an individual to exposure of the GDD. As such, the finding that women are at increased risk for exposure is even more robust.

To our knowledge, this is the largest series of GDD surgeries reported which includes a variety of types of GDD implants and patch graft materials. As GDD surgeries become an increasingly common event in the management of glaucoma, further study is needed to understand why women are at greater risk of GDD exposure and what can be done to mitigate this risk.

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Risk Factors for Exposure of Glaucoma Drainage Devices

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ABSTRACT

Objectives: The purpose of this study was to identify risk factors for exposure of glaucoma drainage devices (GDD).

Setting: This retrospective, observational study was conducted in the Eye Clinic of an academic medical center.

Participants: Participants included 1073 consecutive adults who underwent GDD surgery between January 1st, 2005 and January 1st, 2011. Participants were included if chart review indicated GDD surgery during the study period and excluded if at least 12 months of clinical follow-up was not available in the medical record.

Primary outcome measure: The primary outcome measure was exposure of the GDD occurring at least one month after implant surgery. The characteristics of subjects who experienced exposure of the implant were compared to the characteristics of subjects who did not experience exposure.

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The use of glaucoma drainage devices (GDD) to manage glaucoma has increased dramatically over the past two decades. Review of Medicare claims data indicates that the number of trabeculectomy surgeries declined by >50% while the number of GDD surgeries increased by >150% from 1995 to 2004.[1][1] The Tube Versus Trabeculectomy Study has provided evidence that GDD surgery can be at least as effective as trabeculectomy at reducing intraocular pressure and the need for further surgery over a five year time frame.[2][2] Unfortunately, GDD surgery is not without complications, including erosion of the device through the conjunctiva. Reported rates of GDD exposure in adults range from 3-8% over the first 1-5 years following implant surgery.[3-7][3-6] Exposure of the GDD puts the patient at risk for potentially devastating infection;[8][7] as such, exposure of a GDD warrants surgical revision. Revision of the exposed GDD, however, is challenging. In one large series of revision surgeries for GDD exposure, almost half required additional surgeries following the revision and more than 10% eventually required removal of the implant.[9][8]

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The primary outcome for this investigation was GDD exposure. Exposure of the GDD was defined as clinical recognition of exposure of any part of the device occurring more than one month following surgery and requiring repair. We focused on exposure events occurring greater than one month after surgery to differentiate exposure from operative wound dehiscence. The number of months between the initial surgery and exposure was noted. Descriptive statistics were derived, including means, medians, and standard deviations. The associations between potential explanatory factors and the outcome of exposure were analyzed with logistic regression, testing for interactions when appropriate. Odds ratios and confidence intervals were calculated. Survival analysis was used to compare the time to exposure for specific explanatory variables. We analyzed the data using SAS/STAT® software (SAS Institute, Inc., Cary, North Carolina). In all cases, a p value of <0.05 was considered statistically significant.

RESULTS

Between January 1st, 2005 and January 1st, 2011, 1738 GDD surgeries were performed on 1411 adults at the Duke Eye Center. Excluding cases with less than 12 months of follow-up resulted in 1073 individual GDD surgeries for review. During the study period, 67 of these 1073 GDD implants were noted to have become exposed. The characteristics of the total sample and the cases of exposure are described in the Table.

Characteristics of subjects and association with glaucoma drainage device exposure by univariable analysis

Subject Characteristics (n=1073)	Total number (%)	Number with exposure (%)	p-Value	Odds ratio [95% Confidence Interval]
Gender				
Male	483 (45)	20 (4)	0.011	2.00 [1.17-3.43]
Female	590 (55)	47 (8)		
Race				
White	550 (51)	43 (8)	0.044[a]	1.69 [1.01-2.83]
Black	503 (47)	24 (5)		
Other	20 (2)	0		
Diabetes				
Present	300 (28)	23 (34)	0.296	0.76 [0.45-1.28]
Not present	711 (66)	42 (63)		
Unknown	62 (6)	2 (3)		
Uveitis				
History of uveitis	209 (20)	8 (12)	0.410	0.78 [0.44-1.40]
No history of uveitis	649 (60)	47 (70)		
Unknown	215 (20)	12 (18)		
Glaucoma drainage device				
Ahmed	598 (56)	43 (7)	0.203[a]	0.67 [0.42-1.16]
Baerveldt	470 (44)	24 (5)		
Molteno	4 (<1)	0		
Shocket	1 (<1)	0		
Patch graft material				
Eye bank sclera	591(55)	43 (7)	0.174[a]	1.50 [0.85-2.65]
Tutoplast® sclera	363 (34)	18 (5)		
Sclera NOS[b]	75 (7)	4 (5)		
Single-layer Tutoplast® pericardium	39 (4)	2 (5)		
Double-layer Tutoplast® pericardium	14 (1)	0		
Unknown	1 (<1)	0		
Location				
Superior	991(92)	62 (6)	0.955	1.03 [0.40-2.63]
Inferior	82 (8)	5 (6)		
Total number of glaucoma drainage devices in eye				
One	817 (76)	49	0.125[c]	0.65 [0.37-1.13]
Two	175 (16)	16		
Three	24 (2)	2		
Four	1 (<1)	0		

	Value		p-Value
Age (years, mean±SD; median)	64±16; 66	65±16; 69	0.335

[a]p-values and odds ratios derived from Fishers Exact test for comparison of exposure for italicized variables (other variables in that category with insufficient data points for analysis) .

[b]NOS = not otherwise specified

[c]p-value for comparison of a single glaucoma drainage device versus multiple glaucoma drainage devices in the same eye.

The duration of follow-up after GDD surgery ranged from 12 to 84 months, mean 41 months, median 37 months. The GDD implantation surgeries were performed by 10 different glaucoma fellowship-trained surgeons and there was not a significant association between individual surgeon and likelihood of GDD exposure (p=0.202). In univariable analyses of potential explanatory variables including type of GDD, type of patch graft, total number of GDD in the eye, and location of GDD, only female gender (p=0.011) and white race (p=0.044) were associated with likelihood of exposure (Table). Women having undergone GDD surgery had twice the odds of experiencing exposure than men who underwent GDD surgery (OR 2.00 [95% CI 1.17-3.43]). We considered that the association between gender and exposure might be related to age, as the women in the sample were, on average, older at the time of surgery than the men (mean age of women 66 years, mean age of men 61 years, p=0.001). The test of interaction between age and gender was significant (p=0.025), implying that age influenced the association between gender and exposure differently for women compared to men. As such, separate analyses were performed for men and women with regards to the association between age and exposure, revealing that increasing age was associated with increased likelihood of GDD exposure for men (p=0.038), but not for women (p=0.394).

Multivariable analysis

The interaction between age and race was not significant (p=0.109); as such, age, race, and gender were considered together as explanatory factors for the outcome of exposure. In this multivariable logistic regression model, age was not associated with exposure (p=0.657); whiteblack race (p=0.046) and female gender (p=0.013) remained significantly associated with likelihood of exposure. The odds of a white female experiencing exposure of the GDD were 3.88 times that of a black male experiencing exposure.

Survival analysis

To account for duration of follow-up, the relationship between potential explanatory variables and the outcome of GDD exposure was also queried by survival analysis. The mean time from GDD implant surgery to GDD exposure was 25±19 months. The mean time to exposure for females was 23±18 months and for males was 31±20 months. Survival analysis revealed that females experienced exposure of the GDD earlier in the course of follow-up than men (p=0.024, Figure). White patients experienced exposure earlier than African American patients (0.026). Survival of the GDD without exposure was not associated with location of the GDD, history of multiple GDD, diabetes, uveitis, type of glaucoma, or type of patch graft used (p=0.239-0.669).

DISCUSSION

Glaucoma drainage device surgery is becoming increasingly common,[1][1] and is a valuable tool in the management of glaucoma. Exposure of the implant, however, is one of the more frequent[2-4 6][3-6] and challenging complications of GDD surgery.[8 9][7-8] To better inform both surgeons and patients about the risks and benefits of GDD surgery, we need a clearer understanding of the risk factors associated with exposure of the implant.

Most of the studies which have provided evidence for rates of GDD exposure have included only one type of implant, such as the Baerveldt,[6 7] [2, 6][3-5] or Ahmed.[4 10][6-10] One study of exposure outcomes included both Baerveldt and Ahmed implants but focused primarily on outcome differences based on patch graft materials.[11][11] Another recent study included multiple types of implants and did not find a difference in exposure rates.[3] Our study included 598 (56%) Ahmed and 470 (44%) Baerveldt GDD implants. We did not find a difference in exposure outcomes related to type of GDD: 43 (7%) of the subjects with Ahmed implants experienced exposure compared to 24 (5%) of the subjects with Baerveldt implants (p=0.203). Exposure rates for both types of implants fell within the range of exposure rates previously published.[3-7] [3-6]

Previous studies have compared the exposure-related outcomes for specific patch graft materials and found that single-layer pericardium is associated with greater risk of exposure than double-layer pericardium[13][11] and pericardial patch grafts in general are associated with greater likelihood of exposure than corneal patch grafts.[12][12] Some studies, however, have failed to find an association between patch graft material and exposure rates.[3 4][4] In our study, a variety of patch graft materials were employed: primarily eye bank sclera (n=591, 55%), Tutoplast® (IOP Ophthalmics, Costa Mesa, California) sclera (n= 363, 34%) and to a lesser extent, single (n=39, 4%) and double-layer (n=14, 1%) Tutoplast® pericardium. The numbers of subjects receiving pericardial patch grafts were too small for adequate analysis, but there were no incidences of exposure in our double layer pericardial patch group as there were none in the 59 cases in Moster's study.[13][11] We did not find an association between

the likelihood of exposure for subjects receiving eye bank sclera (n= 43 exposure, 7%) compared to subjects receiving Tutoplast® sclera (n= 18 exposures, 5%; p=0.174). Although failure to detect a difference does not mean that a differential likelihood of exposure does not exist, given the similar rates of exposure between subjects with eye bank sclera and subjects with Tutoplast® sclera, a much larger sample would be needed to detect significant difference. For example, based on the rates of exposure in our study , we estimate that 2327 subjects receiving eye bank and 2327 subjects receiving Tutoplast® sclera would be needed to have 90% power to detect a significant difference in likelihood of exposure, with α=0.05.

Reports of GDD exposure related to location of the implant have varied. In a series of Ahmed GDD surgeries, implants placed in the inferior quadrants were more likely to expose than implants located superiorly.[10][10] Another study of Ahmed implants, however, found higher rates of early wound dehiscence for GDD implants located inferiorly, but no association between location and later GDD exposure.[11] [9] We also did not find a difference in exposure for inferior (n= 5 exposures, 6%) versus superior location of the device (n= 62 exposures, 6%; p=0.955). Furthermore, we did not find a difference in the likelihood of exposure for GDD implants in eyes with a single implant (n= 49 exposures, 6%) compared to eyes with pre-existing GDD prior to the surgery included in the study (n= 18 exposures, 9%; p= 0.125). We purposely, however, only considered the first GDD surgery within the study period for each subject, so it is possible that we underestimated the rates of exposure for subjects with multiple implants by excluding subsequent GDD surgeries and exposure events in the same subject. We did not investigate concurrent ophthalmic surgery as a risk factor for GDD exposure, although this has recently been reported to be a significant factor associated with GDD exposure.[3]

We observed that women had twice the odds of experiencing exposure of the GDD compared to men. In attempts to understand this association, we considered that this finding may be confounded by age, as the women in the study population were, on average, older at the time of surgery than the men. Indeed, the test of interaction between age and gender with regards to likelihood of GDD was significant, indicating that age influences the likelihood of exposure differently for men and women. For men, increasing age inferred a greater likelihood of exposure; multivariable analysis revealed that women, however, were more likely to experience exposure of the GDD than men regardless of age. Moreover, in survival analysis, women experienced GDD exposure earlier in the course of follow-up than men. A gender-related difference in GDD exposure is a new finding: in a study of 11 cases of GDD exposure and 44 subjects with GDD and without exposure, age and gender were not related to likelihood of exposure of the device.[4][6] Likewise, in a recent study of 339 eyes of 332 subjects with GDD surgery including 28 eyes with GDD exposure, gender was not associated with

likelihood of exposure.[3] Our study, however, defined exposure as occurring at least one month post-operatively, and it is possible that female gender is a more important risk factor for later exposure than in early would dehiscence. The number of subjects included in our study is also , however, substantially larger, improving our power to detect outcome differences.

We found that white race (compared to black race) was associated with greater likelihood of GDD exposure, although the association was not as strong (OR 1.69 [95% CI 1.01-2.83]). When considered together in a multivariable model, white race (p=0.046) and female gender (p=0.013) remained significantly associated with GDD exposure. In a recent case control study of GDD exposures, Koval et al found Hispanic race (versus non Hispanic ethnicity including black and white subjects), to be a risk factor for exposure.[14] Our study population did not include enough persons of Hispanic descent for analysis. Koval and colleagues matched controls to cases based on gender, so the influence of gender on exposure risk as not explored. Although, to our knowledge, no previous studies have found black race to be a risk factor for primary exposure of the GDD, interestingly, black race was a risk factor for requiring multiple surgeries following repair of GDD exposure in a series of exposure cases.[9][8] The same study also found diabetes to be a risk factor for failure of primary revision of an exposed GDD. We did not find an association between diabetes and GDD exposure. Presence or absence of diabetes was determined by review of the problem list in our study, rather than laboratory tests, and some subjects with diabetes may have been classified as nondiabetics. Consistent with our findings, however, investigators in Korea did not find an association between diabetes and GDD exposure.[4][6]

We considered potential factors that might explain the increased likelihood of GDD exposure in women. Friction of the implant against the ocular tissues may contribute to late exposure of the GDD. In general, the orbital dimensions of women are smaller than men, with lower average height of the orbit and width of the orbital fissure for women compared to men.[16][14] Rates of GDD exposure are higher in children than in adults, supporting the theory that a "tight" orbit is associated with increased likelihood of exposure.[17][15] A mechanically tighter orbit may contribute to the racial differences in exposure outcomes noted in our study. On average, the palpebral fissure width is greater for blacks than for whites.[18][16]

Repetitive microtrauma may compromise conjunctival integrity, increasing the risk for exposure. Ocular dryness may exacerbate friction between the eyelids and ocular surface. The median age at surgery for the subjects in our study was 66 years, suggesting that many women were post-menopausal and may have hormone-related dry eye syndrome. A prospective study quantifying dry eye in patients undergoing GDD surgery may help determine if dry eye influences the association between female gender and GDD exposure.

Our study has several limitations. Some patients may have experienced GDD exposure more than one year after surgery and have been treated elsewhere. Our dataset was limited to the history in the medical record and documentation may not always be complete. For example, we did not find an association between uveitis and exposure. The history of uveitis may not have been recorded for every patient, however. In children, uveitis is a risk factor for GDD exposure.[17] [15] Likewise, we could not examine the contribution of dry eye disease. Similarly, we limited our surgical history to previous GDD surgeryglaucoma surgeries; other prior conjunctival surgeries may be associated with GDD exposure, but was not uniformly recorded for each subject, especially subjects who may have had surgeries prior to treatment at our institution.

We purposefully limited our study to cases of exposure occurring more than one month from surgery to exclude operative wound dehiscence; accordingly, the findings should not be extrapolated to include early exposures. Indeed, other studies have found alternative risk factors for early wound dehiscence.[11][9] We chose to exclude repeat surgeries in the same patient in order to not over-represent patient-specific characteristics which might predispose an individual to exposure of the GDD. As such, the finding that women are at increased risk for exposure is even more robust.

To our knowledge, this is the largest series of GDD surgeries reported which includes a variety of types of GDD implants and patch graft materials. As GDD surgeries become an increasingly common event in the management of glaucoma, further study is needed to understand why women are at greater risk of GDD exposure and what can be done to mitigate this risk.
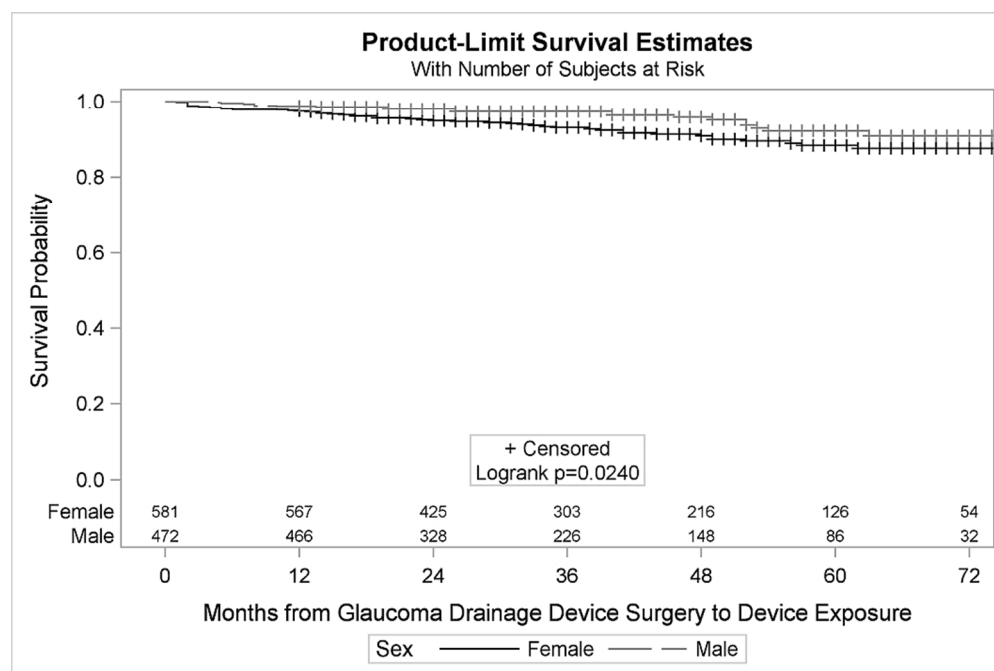
ACKNOWLEDGEMENTS

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Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival probabilities for tube exposure for females and males
90x60mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract ✓	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale ✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives ✓	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design ✓	4	Present key elements of study design early in the paper
Setting ✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants ✓	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables ✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement ✓	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias ✓	9	Describe any efforts to address potential sources of bias
Study size ✓	10	Explain how the study size was arrived at
Quantitative variables ✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods ✓	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results

Participants ✓	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data ✓	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data ✓	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results ✓	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses ✓	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results ✓	18	Summarise key results with reference to study objectives
Limitations ✓	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation ✓	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability ✓	21	Discuss the generalisability (external validity) of the study results

Other information

Funding ✓	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.